

Letter to the Editor

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Letter by Menzaghi et al Regarding Article, “Plasma Levels of Fatty Acid–Binding Protein 4, Retinol-Binding Protein 4, High-Molecular-Weight Adiponectin, and Cardiovascular Mortality Among Men With Type 2 Diabetes: A 22-Year Prospective Study”

To the Editor:

We read with interest the article on the paradoxical association between high-molecular-weight (HMW) adiponectin and cardiovascular mortality in men with type 2 diabetes mellitus from the HPFS (Health Professional Follow-Up Study).¹ These data resemble those we have previously reported² in men with type 2 diabetes mellitus, comprising a large subset of the same HPSF and additional Italian individuals.²

To address whether such association is sustained by a cause–effect relationship, a genetic risk score (GRS) built on 19 single nucleotide polymorphisms previously associated with adiponectin levels (Mendelian randomization) was used.¹ Notably, GRS was not associated with cardiovascular mortality, thus speaking against a causal role of HMW adiponectin on it. This finding is in marked contrast with our recent report, showing a significant association between rs832354 (a single nucleotide polymorphism strongly associated with HMW adiponectin³) and cardiovascular mortality in type 2 diabetes mellitus patients of both sexes.⁴ Of note, our association was entirely driven by males (ie, no association observed among females),⁵ thus coincidentally reinforcing the belief of a sexual dimorphic effect of serum adiponectin on cardiovascular mortality² and further stressing the difference with Liu et al¹ report.

Here, we address some possible causes of such strident discrepancy.

First, differences in the clinical set may have played a role. In fact, although in HPFS only 50% patients had baseline cardiovascular disease, all our patients had established coronary artery disease.⁴ That this difference may be important is suggested by the observation that when in HPFS participants with baseline cardiovascular events were excluded, the hazard ratio (95% confidence interval) of cardiovascular mortality of patients with high HMW adiponectin decreased from 2.07 (1.42–3.06) to 1.39 (0.54–3.61),¹ a 54% reduction in a log scale. It is, therefore, likely that in the absence of baseline cardiovascular disease, the deleterious effect of adiponectin on cardiovascular mortality is attenuated, thus making difficult addressing causality.

Second, also differences in environmental and genetic background across studies have to be considered. In fact, HPFS patients were recruited from all over the United States, whereas ours were all recruited in a very small and homogeneous region of Central Southern Italy. In addition, whereas our participants were all Whites,⁴ those of HPFS were not.¹ Because genetic background of serum adiponectin is heterogeneous across ethnicities,⁶ such difference too may have contributed to discrepancy between the 2 studies.

Third, statistical power is important to make reliable Mendelian randomization studies.⁷ Unfortunately, in Liu et al¹ article, no power was reported for the association between GRS and cardiovascular mortality. Because GRS was barely associated with HMW adiponectin ($P=0.02$),¹ the risk of false-negative findings on its association with cardiovascular mortality has to be seriously considered.

Finally, it seems, also by the reference quoted (ie, 29, which reports a case–control study), that a logistic rather than a Cox regression was used when analyzing the association between GRS and cardiovascular mortality.¹ If this is the case, ignoring time to event could have altered the results and contributed to the discrepancy with our study.

In all, disentangling the intrinsic nature of the paradoxical association between adiponectin and cardiovascular mortality in type 2 diabetes mellitus is a difficult task; further collaborative studies, in extensively phenotyped patients of different ethnicities from well-powered samples, are definitely needed to accomplish it.

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Disclosures

None.

Claudia Menzaghi

Research Unit of Diabetes and Endocrine Diseases
IRCCS Casa Sollievo della Sofferenza
San Giovanni Rotondo, Italy

Massimiliano Copetti

Unit of Biostatistics
IRCCS Casa Sollievo della Sofferenza
San Giovanni Rotondo, Italy

Vincenzo Trischitta

Research Unit of Diabetes and Endocrine Diseases
IRCCS Casa Sollievo della Sofferenza
San Giovanni Rotondo, Italy
and
Department of Experimental Medicine
Sapienza University of Rome
Italy

References

1. Liu G, Ding M, Chiuve SE, Rimm EB, Franks PW, Meigs JB, Hu FB, Sun Q. Plasma levels of fatty acid–binding protein 4, retinol-binding protein 4, high-molecular-weight adiponectin, and cardiovascular mortality among men with type 2 diabetes: a 22-year prospective study. *Arterioscler Thromb Vasc Biol*. 2016;36:2259–2267. doi: 10.1161/ATVBAHA.116.308320.
2. Menzaghi C, Xu M, Salvemini L, De Bonis C, Palladino G, Huang T, Copetti M, Zheng Y, Li Y, Fini G, Hu FB, Bacci S, Qi L, Trischitta V. Circulating adiponectin and cardiovascular mortality in patients with type

- 2 diabetes mellitus: evidence of sexual dimorphism. *Cardiovasc Diabetol*. 2014;13:130. doi: 10.1186/s12933-014-0130-y.
3. Qi L, Menzaghi C, Salvemini L, De Bonis C, Trischitta V, Hu FB. Novel locus FER is associated with serum HMW adiponectin levels. *Diabetes*. 2011;60:2197–2201. doi: 10.2337/db10-1645.
 4. Ortega Moreno L, Copetti M, Fontana A, De Bonis C, Salvemini L, Trischitta V, Menzaghi C. Evidence of a causal relationship between high serum adiponectin levels and increased cardiovascular mortality rate in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2016;15:17. doi: 10.1186/s12933-016-0339-z.
 5. Menzaghi C, Salvemini L, De Bonis C, Bacci S, V. Trischitta. High molecular weight adiponectin (HMW-a) and cardiovascular (CV-) death in patients with type 2 diabetes (T). *Diabetes*. 2013;62(suppl 1):A114.
 6. Dastani Z, Hivert MF, Timpson N, et al; DIAGRAM+ Consortium; MAGIC Consortium; GLGC Investigators; MuTHER Consortium; DIAGRAM Consortium; GIANT Consortium; Global B Pgen Consortium; Procardis Consortium; MAGIC investigators; GLGC Consortium. Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. *PLoS Genet*. 2012;8:e1002607. doi: 10.1371/journal.pgen.1002607.
 7. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27:1133–1163. doi: 10.1002/sim.3034.